Module 8
Organs and Organisms

- Early and late effects (malignancy and genetic problems) will be explored.
- The effects of radiation on the organs and the organism will be addressed using examples from medicine and various occupations.
- Carcinogenesis is a *late stochastic effect*, as compared to the late nonstochastic effects from the previous module.
- Various theories of carcinogenesis will be examined in the context of ionizing radiation.
- The effects to be studied are *non-threshold, non-dose-response relationships*.

Early Stochastic Effects (1)

- The most devastating human response to radiation is death, which occurs at a minimum dose of 100 rads (1 gray) with a whole body.
- Acute radiation lethality is an early effect of radiation not commonly encountered in diagnostic radiology.
- Acute radiation lethality is measured by the $LD_{50/30}$ in humans and animals.
- The $LD_{50/30}$ is the dose of radiation to the entire body which will result in death within 30 days to 50% of the subjects irradiated.

Early Stochastic Effects (2)

- The LD_{50} is the dose of any agent or material thatcauses a mortality of 50% in the experimental groups within a specified period of time.
- The LD_{50} is a convenient way to smooth out the problems of heterogeneous populations, by reducing the skewing effects due to extreme subjects.
- The peak incidence of death for humans occurs from days 30-60. Therefore, $LD_{50/60}$ is more commonly used for humans, rather than the $LD_{50/30}$ which is more often used with animals.
- However, the $LD_{50/30}$ is the most convenient form of the expression.

Early Stochastic Effects (3)

- The best estimate for $LD_{50/60}$ for humans is 3.25 Gy or 325 rem for young, healthy adults.

- This reflects the observation that larger species are more susceptible to hemopoietic damage than are smaller species.
- As the whole-body irradiation dose increases, the average time between exposure and death decreases.

- This time is known as the ***mean survival time***. In doses above 500 rem, death from hemopoietic syndrome 3-4 weeks later is common. Survival may be possible if infection, bleeding, or physical trauma are avoided during the blood cell nadir.

- Bone marrow transplants have been used to try to “rescue” patients who have eceived a dose between 800-1000 rads.

Acute Radiation Syndrome (1)

- The early stochastic effects of radiation are found in acute radiation syndrome.

- Early radiation lethality is defined as death occurring within a few weeks that can be attributed to a specific high-intensity exposure to radiation.

- Thirty people died of acute radiation exposure at Chernobyl in April 1986. (Much of the recent information on dose levels were obtained by the Chernobyl accident in 1986.)

- The syndrome consists of three stages—prodromal stage, latent period, and manifest illness stage.

Acute Radiation Syndrome (2)

- The nature of radiation lethality, the timing of death, and whether death occurs at all *depends upon various cell populations*, specifically their depletion and their ability to recover to a normal level.

- It is the balance between the gradual removal of the aging mature cells and the arrival of the new mature cells that will determine whether the tissue remains intact enough for continued integrityof the tissue and the life of the affected human.

Acute Radiation Syndrome (3)
prodromal stage

- The *prodromal* stage, occurring from a few hours after the irradiation to day one or two, consists of acute symptoms, which last for a limited period of time.
- This period can extend for four weeks.
- The various symptoms of this syndrome vary with respect to the time of onset, maximum severity, and duration, depending on the size of dose.
- Often a severe prodromal response indicates a poor clinical prognosis.
- Symptoms include both gastrointestinal and neuromuscular symptoms.

Acute Radiation Syndrome (4)
latent period

- During the *latent* period, the patient will be free of visible effect.

- The lethal effects of the manifest illness stage are developing even though the patient appears symptom free.

Acute Radiation Syndrome (4)
manifest illness

- During the *manifest illness* stage, the clinical signs and symptoms occur.
- There is a decrease in red blood cells, white blood cells, and platelets.
- This is due to the radiation's effect on the precursor blood cells.
- The gastrointestinal symptoms are nausea, vomiting, and diarrhea
- The diarrhea and dehydration are due in part to the destruction of the villus cells.
- Neuromuscular symptoms include apathy, sweating, fever, and headache.

Syndromes of Acute Radiation Exposure

- *hematopoietic syndrome* ~ 300-900 rads 0.3 - 0.9 gray

- *gastrointestinal syndrome* ~ 500-1200 rads 0.5 - 1.2 gray

- *cerebrovascular syndrome* ~ 10 K-100 K rads 10 - 100 gray

Hematopoietic Syndrome

- The symptoms occur later because mature circulating cells die off and are not then re-supplied by the destroyed precursor population.
- The first phase is due to the lesions of the blood forming organs, leading to hemorrhage and anemia.
- The bone marrow, spleen, and lymph nodes atrophy.
- During 5-6 weeks, infection is important due to destruction of lymphocytes and granulocytes, lack of antibody production, and ulcerations permitting bacteria entry.
- If the patient survives, convalescence begins after two months.

Gastrointestinal Syndrome (1)

- Death may result 5-8 days after irradiation.
- This syndrome predominates at low whole-body doses, in particular doses to the abdomen.
- The symptoms include nausea, vomiting, prolonged diarrhea, dehydration, weight loss, and complete exhaustion.
- Death is due to destruction of the functioning cells of the villi in the small intestine.

Gastrointestinal Syndrome (2)

- Loss of the intestinal barrier leads to a bacterial invasion of the bloodstream and the peritoneal cavity, release of proteolytic enzymes, and the loss of water and electrolytes.
- Symptoms of gastrointestinal origin may disappear after 2-3 days and recur by the fifth day due to loss of the intestinal cells. At this time, peristalsis will end and severe paralytic ileus may occur.
- Circulation failure, coma, and death may follow.
- However, some victims may survive this phase due to fluid replacement therapy and antibiotic treatment.

Cerebrovascular Syndrome

- The *cerebrovascular syndrome* results in death 24-48 hours after exposure.
- The modes of death in the gastrointestinal and hemopoietic syndromes are due to the depletion of stem cells of a critical selfrenewing tissue.
- The exact cause of death in the cerebrovascular syndrome is unclear.
- Some believe neuronal damage secondary to vascular damage, edema, and increased intracranial pressure may cause the symptoms.
- At doses which bring on this syndrome, all three syndromes will occur given enough time; however, the cerebrovascular damage brings death very quickly before the other syndromes are observed.
- This symptoms again include the loss of movement, respiratory distress, disorientation, seizures, and coma.

Prognosis (1)

- In general, prodromal nausea and vomiting are more prolonged at high doses.
- Early CNS symptoms indicate a very high and lethal dose. The longer an individual survives after the first 2-3 weeks, the better the prognosis.
- Those showing the CNS syndrome will die.
- Those with continual nausea, vomiting, and diarrhea will probably die.

Prognosis (2)

- Those with brief nausea and vomiting will probably survive.
- The very young and the very old are more radiosensitive than the middle-aged and young adults. Females are also more radioresistant than males.
- The three syndromes of acute radiation syndrome require different levels of radiation for their emergence.

Prognosis (3)

- The lymphocyte count is valuable as a criterion for judging radiation injury.
- The total white cell count is of particular value for following the patient throughout the course of the syndrome.
- When only the lower body is irradiated, a higher dose is tolerated and the gastrointestinal tract is the primary target.

Prognosis (4)

- Survival is more likely if the radiation dose is protracted and if only part of the body is exposed.
- When a very large volume of tissue is irradiated, damage will be evident after a relatively low dose

Table 9-1. Major Forms of Acute Radiation Syndrome in Humans			
Time after Irradiation	**Cerebral and Cardiovascular form (20,000 rad)**	**Gastrointestinal form (2000 rad)**	**Hemopoietic form (400 rad)**
First day	nausea vomiting diarrhea erythema disorientation agitation ataxia weakness somnolence coma convulsions shock death	nausea vomiting diarrhea	nausea vomiting diarrhea
Second week		nausea vomiting diarrhea fever emaciation prostration death	
Third and fourth weeks			weakness fatigue anorexia nausea vomiting fever hemorrhage epilation recovery(?)

Major Forms of Acute Radiation Syndrome in Humans

Time after Irradiation	**Cerebral and Cardiovascular form (20,000 rad)**	**Gastrointestinal form (2000 rad)**	**Hemopoietic form (400 rad)**
First day	Vomiting, diarrhea, erythema, Disorientation, Agitation, ataxia, Weakness, Somnolence, Coma, Convulsions, Shock, Death	nausea vomiting diarrhea	nausea vomiting diarrhea

Major Forms of Acute Radiation Syndrome in Humans

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Major Forms of Acute Radiation Syndrome in Humans

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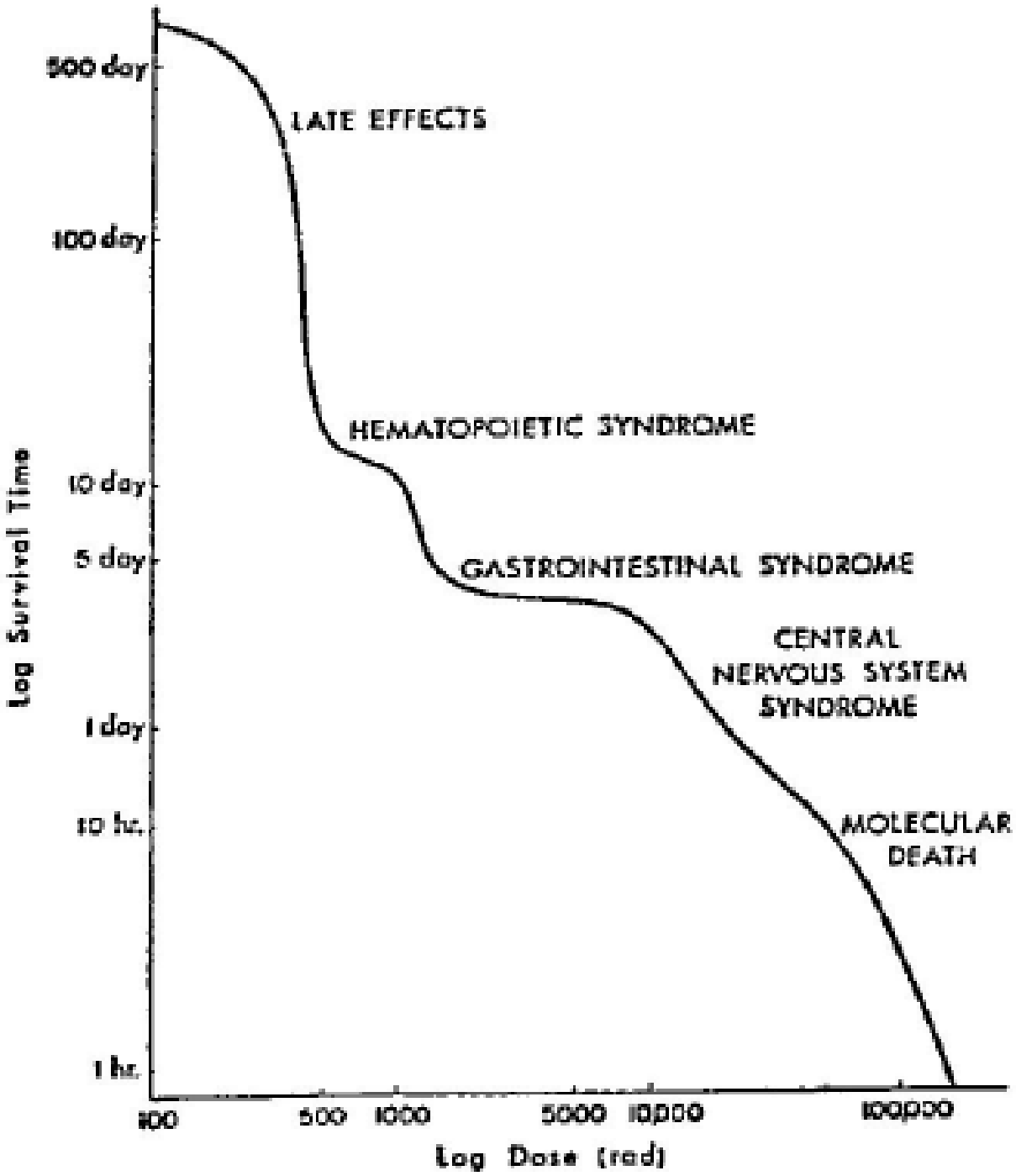
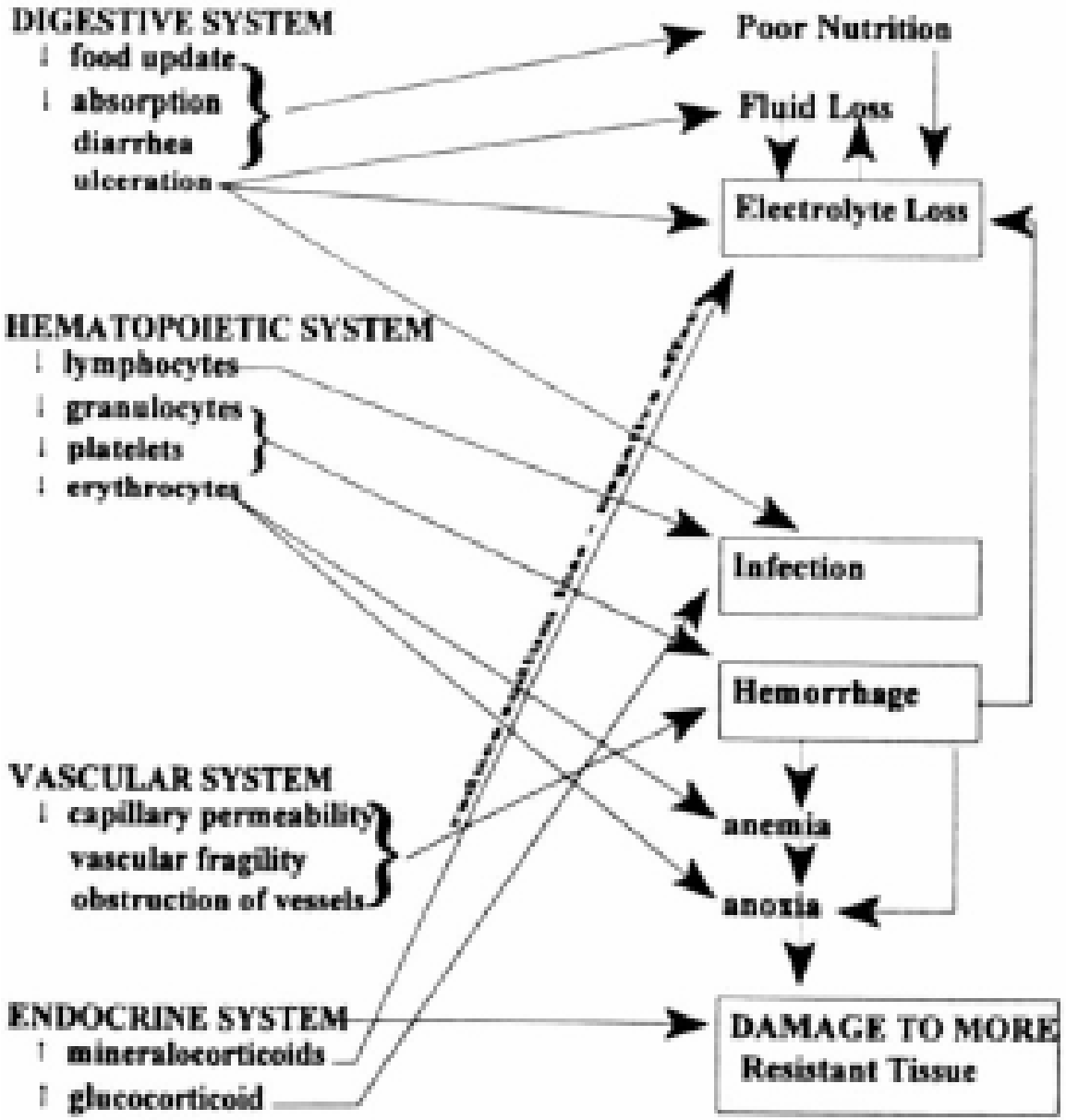

500 day
100 day
10 day
5 day
1 day
10 hr.
1 hr.
Log Survival Time
LATE EFFECTS
HEMATOPOIETIC SYNDROME
GASTROINTESTINAL SYNDROME
CENTRAL
NERVOUS SYSTEM
SYNDROME
MOLECULAR
DEATH
100
500
1000
5000
10000
100000
Log Dose (rad)



The response to radiation is noted with the arrows. An up arrow means increase in that factor with irradiation and a down arrow means a decrease in that factor with irradiation.

Adapted from R. F. Yaffe and G. L. Holgreen, *Practical Health Physics*, California Book Company, Berkley 1971.

Biological Effects as a function of dose (1)

0.001 r/day	Natural Background Radiation
0.01 r/day	Permissible dose range, 1957
0.1 r/day	Permissible dose range, 1930-1950
1.0 r/day	Illness in 3 to 6 months [not certain] Death in 3 to 6 years [extrapolation from animal data]
10 r/day	10 r/day Illness in 3 to 6 weeks [not certain] Death in 3 to 6 months [extrapolation from animal data]
10 r instantaneously	Few or no effects

Biological Effects as a function of dose (2)

10 r instantaneously	Few or no effects
10^2 r instantaneously	Mild irradiation sickness in some people No death
10^3 r instantaneously	Disruption of the blood forming and gastrointestinal tissue 100% death in 30 to 60 days.
10^4 r instantaneously	Disruption of the central nervous system Death in minutes to hours
10^5 r instantaneously	Spastic seizures, sperm mobility ceases Death in seconds

Late Stochastic Effects – Carcinogenesis (1)

- Cancer is a gross distortion of cell behavior caused by numerous gene mutations and numerous abnormalities in the production and functioning of proteins.

- Cancer is a class of diseases, all pertaining to unlimited cell growth that is potentially fatal.

- Cancer initiates from a single cell that has been transformed due to a particular change in its DNA.
- Ninety percent of human cancers are carcinomas.

Late Stochastic Effects – Carcinogenesis (2)

- A neoplastic cell is hyperresponsive to growth factors, underresponsive to growth inhibitors, and has an increase in metabolic transport capabilities.

- A cancer cell tends to have an irregular shape, an abnormally appearing nucleus, is more mobile, is invasive, and shows genomic instability.

- In a benign tumor, the neoplasm remains as a well-defined cluster and does not spread to neighboring cells.

- A malignant tumor is capable of invading surrounding tissues, due to ***disruption of intracellular adhesion***, which enables invasive tumor cells to insert themselves between cells of surrounding tissue and to migrate.

- As it spreads throughout the body, the tumor can invade and destroy tissue until the organism is so compromised that death results.

Late Stochastic Effects – Carcinogenesis (3)

- Carcinogenesis is the primary late effect of radiation.
- Unlike early effects which are due to the radiation's effect on division, the late effects are possibly due to changes within the cell's DNA or microvasculature.
- Radiation carcinogenesis has mainly been studied in experimental animals, such as the landmark study by Furth & Furth (1936) on mice.
- However, carcinogenesis in various occupational groups, which will be described later in the lesson, do demonstrate the stochastic nature of cancer.
- These and other studies have led to a dose-response curve (Hall: Figure 10-5, page 152).
- The graph shows that incidence vs. dose curve rises sharply for low doses.
- There is a maximum value of incidence above which incidences decrease.
- At this saturation point, the number of cells remaining alive to produce a tumor are greatly reduced.

Late Stochastic Effects – Carcinogenesis (4)

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Late Stochastic Effects – Carcinogenesis (5)

- However, carcinogenesis in various occupational groups do demonstrate the stochastic nature of cancer.
- There are exceptions to the rule.
- For example, susceptibility to radiation-induced leukemia is constant throughout life; whereas, susceptibility to respiratory cancer *increases* in middle age.

Theories on Cancer Development

- Oncogenes
- Cooperating genes
- Suppressor genes.

Clonal Theory/ Oncogenes (1)

- Although a virus causes cancer by inserting an oncogene from its own genome into that of the cell.
- The mechanism of transformation by radiation is to cause changes in a normal proto-oncogene native to that cell.
- These changes cause the proto-oncogene to be activated.
- The proto-oncogenes are present in every cell and may serve to regulate cell growth and differentiation.
- They act in a dominant manner.
- Cells containing this activated oncogene become transformed, evidenced by a lack of contact inhibition.

Clonal Theory/ Oncogenes (2)

- The radiation causes activation of the proto-oncogenes in three ways:

  - ❖ point mutation,
  - ❖ rearrangement or translocation of a chromosome which places an oncogene near a promoter sequence,
  - ❖ gene amplification.

Clonal Theory/ Oncogenes (3)

- The studies support a three-stage process in the development of cancer due to changes in the proto-oncogene:
  - ❖ Transformation of cell with lack of response to growth control mechanisms,
  - ❖ Invasion of transformed cells to surrounding tissues,
  - ❖ Migration of cells to other body locations to establish a tumor (metastasis).
- This process is known as the *clonal theory*, which assumes that a single radiation interaction alters the DNA of a single cell, thereby producing cancer in the cell.

Clonal Theory Considerations

- Studies on animals and observations of human patients have shown that perhaps the clonal theory is too simplified.
- Levels of hormones are extremely influential in cancers of endocrine glands (ovaries, pituitary, etc.).
- Murineleukemias, leukemia in rats and mice, are dependent on viruses.
- Immunocompetence is an important modifier in the survival of the cancerous cell.

Suppressor Genes Theory

- Normal cells contain a gene to suppress the neoplastic potential of tumor cells.
- This suppressor gene may be located on chromosome 11.
- Mutation of the suppressor gene p53 may result in cancers of the lung, esophagus, breast, liver, and brain.
- Loss of the protein p105Rb may lead to retinoblastoma.
- Somatic homozygosity may also result in an increased incidence of retinoblastoma, colon cancer, etc.
- Most suppressor genes are recessive.

Initiation - Promotion Hypothesis/Cooperating Genes

- There is typically a latency, or waiting period, between the radiation event and the cancer, which depends on the type of malignancy.
- This can be explained by Berenblum's *initiation-promotion hypothesis*.
- The first step—*initiation*—is the step in which the cell is altered or activated.
- During the second step—*promotion*—the exposure of the cell to various agents leads to the expression of the cancer.
- Since the two steps of initiation and promotion are involved in carcinogenesis, two cooperating oncogenes are needed for expression of the malignant phenotype.
- For example, the combination of myc and ras might be required for cancer to develop. Myc oncogenes confer immortality, whereas ras oncogenes confer loss of contact inhibition.

Other Theories of Carcinogenesis

- The somatic-mutation hypothesis deals with the damage of the cell due to radiation.
- The viral hypothesis states the possibility of a virus weakening the cell, thereby leading to vulnerability for cancer development.
- Another similar theory views a virus as the direct cause of the cancer.

Effect of Ionizing Radiation on Cancer

- Ionizing radiation is an activator of oncogenes and an inactivator of tumor-suppressor genes.
- Oncogene activation promotes cellular proliferation, and the checks on this proliferation are removed through the inactivation of tumor suppressor genes.
- Specific oncogenes and tumor suppressor genes have been correlated with specific cancers; therefore, genetic mutations do lead to cancer.
- More than seventy oncogenes and a dozen tumor-suppressor genes have been identified.
- The oncogenes are activated by the mutation or amplification of normal protooncogenes, which are genes that are part of regulatory pathways that exert influence through phosphorylation of target proteins, formation of protein protein complexes, or regulation of transcription of target genes.
- Oncogenes are dominant, positive regulators that stimulate cell growth.
- Oncogenes may be activated through a variety of cytogenic events, such as large chromosome deletions, inversions, and translocation.

Example of oncogenes in Cancer

- For example, the *ras* oncogene is mutated in about 30% of all human cancers, including bladder and colon cancer.
- Human B-cell lymphomas are due to translocation of *bcl-2* proto-oncogenes in 85% of leukemia cases.
- The *cyclin-D1* oncogene is an amplified gene associated with parathyroid cancer.
- The *ret* oncogene is associated with papillary adenocarcinomas of the thyroid, the major type of thyroid cancer found among atomic-bomb survivors, including children affected by the Chernobyl accident.
- The *bcr/abl* oncogene is strongly linked with a major form of radiation-induced B-cell leukemia called chronic myelogenous leukemia.

Role of Tumor Suppressors

- The normal role of tumor suppressor genesis to inhibit cell growth, with their protein products acting as stops on the cell cycle.
- Tumor suppressor genes may be inactivated through the induction of point mutations, chromosome rearrangements, or the loss of part or all of a chromosome.
- The p53 gene, involved in the G1 checkpoint, is mutated in over 50% of all human cancers.
- Mutations of the core domain of the DNA binding region of p53 are correlated with human cancer.
- A mutation of *rb* can lead to retinoblastoma, a rare childhood cancer of the retina.

Radiation (De)Activation

- Most single strand breaks are repaired with only a slight risk of genetic mutation.
- Base alterations and basic sites can cause single base changes known as point mutations, which are easily repaired.
- The double strand break is caused preferentially by ionizing radiation.
- The risk of double strand breaks is low; for example, background radiation levels would produce only one double strand break per 10 cells per year.
- Double strand breaks are difficult to repair and may result in the loss of genetic information.
- A process called homologous recombination may act to restore the double strand break.

Occupational Exposure

- Carcinogenesis in various occupational groups do demonstrate the stochastic nature of cancer.
- The sensitivity for radiogenic cancers varies greatly with the organs affected.
- The two organs now believed to be the most sensitive for cancer are the female breast and the lung.

Radiology

- Radiologists were at much greater risk from the 1930s to 1950s before modern procedures existed.
- Until about 1950, radiologists in the US were observed to have excess cancer mortality, especially leukemia, lymphoma, and multiple myelomas, when compared to practitioners in other medical specialties.
- According to a survey in 1956 of 80,000 obituaries of doctors, the mean age of death of radiologists was
- 60.5 years, as compared to a mean age of 65.7 for doctors not exposed to daily radiation.

Uranium Miners

- One of the decay products of uranium is radon (Rn), which is a gas emanated by the rocks to the air.
- Exposure to radon in the mines leads to lung cancer.
- Radon was inhaled by the miners, depositing atoms of radioactive material in their lungs.
- Studies involving the pitchblende miners in Saxony indicate that alpha radiation produces the tumors in the lungs.
- The average exposure of the miners is 15-20 years.
- One study of uranium miners around the world showed an 80% increase in lung cancer deaths over what was seen in unexposed miners.

Radium Dial Painters

- In the 1920s and the 1930s, watch dials were painted with luminous paints containing radium.
- This led to bone cancer due to the intense alpha radiation.
- The radium behaved chemically as calcium and was deposited in the bone.
- This group of workers had bone sarcomas and carcinomas of the epithelial cells of the sinuses.
- It was the dangers faced by the radium-dial painters which revealed the danger of occupational exposure to radiation.
- In one study of this population, of 154 subjects who received skeletal doses of greater than 20,000 rem, 62 subjects developed skeletal tumors.

Radium Injections

- Excess cancer was also due to injection of radium, which was widely taken in Germany (1944-1951) for its alleged curative power.

- The radium was later deposited in bone, leading to an incidence of bone sarcoma 280 times that of anunexposed population.

Ankylosing Spondylitis

- Ankylosing spondylitis is a disease of the spine.
- This arthritis-like condition, in which patients walk hunched over, was treated by radiation in the 1940s and1950s in Great Britain.
- There is a higher risk of leukemia in these patients.
- These patients also had increased malignancy due to non-Hodgkin's lymphomaand cancers of the esophagus, lung, bone, breast, and brain.

Women with Tuberculosis

- Women, in both Nova Scotia and New England, received fluoroscopic therapy for tuberculosis and now have a higher rate of breast cancer.

- Patients receiving radiotherapy for postpartum mastitis also showed an excess incidence of breastcancer.

Children with Enlarged Thymus

- Thymic enlargement was treated with radiation in two populations of children in the 1940s and 1950s in Ann Arbor, Michigan, and Rochester,New York.

- Twenty years after irradiation of the thymus, an increase occurred in the rate of thyroid cancer. Both malignant and benign thyroid tumors have been observed.

- Thyroid cancer has also been observed in those with tinea capitis (ringworm of the scalp), a condition once treated with X-rays.

In Utero Diagnosis

- The embryo becomes less sensitive to radiation effects as development moves on but is most sensitive during the first trimester (organogenesis).

- Radiation causes an increase in childhood malignancy, mental retardation, skeletal and organ abnormalities, and central nervous system problems.

- Studies indicate a strong link between excess incidence of leukemia and children irradiated in utero.

Nuclear Weapon Detonation *Hiroshima and Nagasaki (1)*

- The best study on radiation induction of cancer in humans is the Life-Span Study of Survivors of the atomic bomb attacks on Hiroshima and Nagasaki, which followed 80,000 individuals over the period 1958-1987.

- These subjects represent all ages, both sexes, and a wide range of doses. Of this population, only 0.35% (500 people) died from radiation-induced solid cancers.

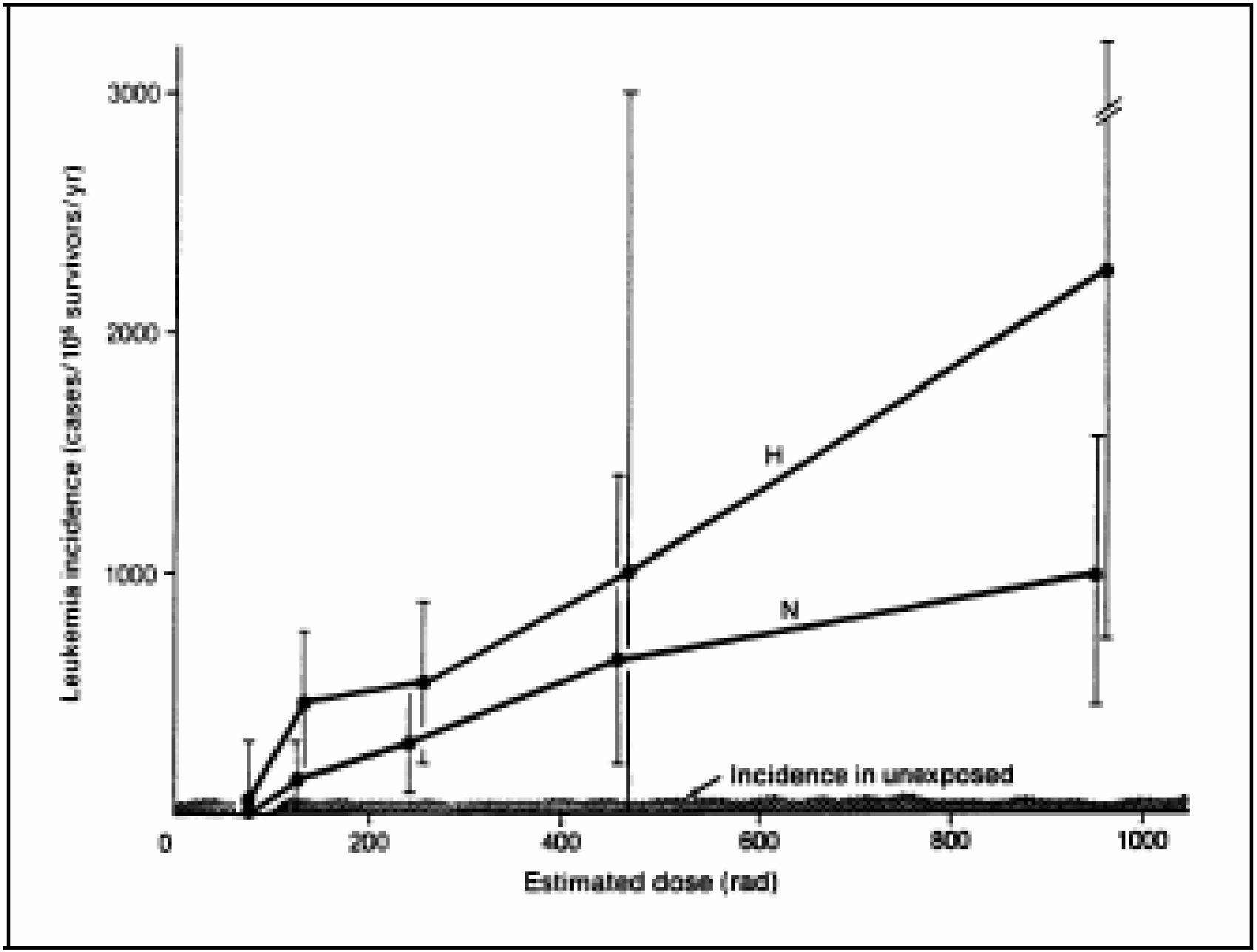
- Similarly, only 0.087% (75 people) have developed radiation-induced leukemia.

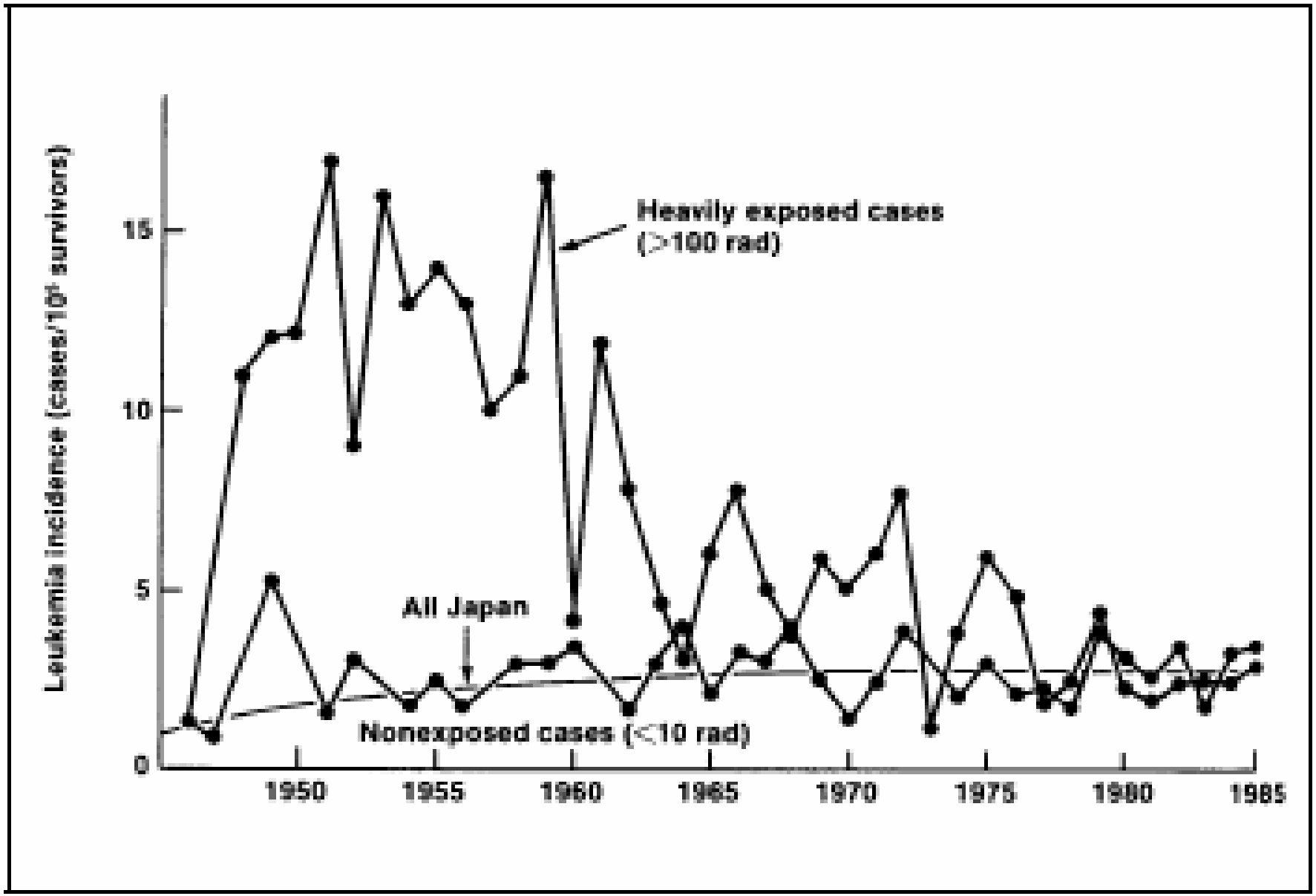
- Statistically significant non-carcinogenic prenatal effects have been observed, including severe mental retardation, small head size, and low intelligence scores.

- The IQ downward shift in embryos, during 8-15 weeks after conception, is estimated to be approximately 30 IQ points per 100 rem.

Nuclear Weapon Detonation
Hiroshima and Nagasaki (2)

- Hiroshima and Nagasaki survivors have a statistically significant increase in leukemia, breast, thyroid, and skin cancer.
- There was a great increase in incidence of leukemia in the residents of these cities after the dropping of the bomb, having its peak incidence five years afterward.
- Of nearly 300,000 people, 100,000 were killed from the blast and its early effects.
- Of the survivers, 100,000 were unaffected, whereas the remainder suffered from lateeffects (leukemia, breast cancer).
- There was a fifteen percent increase in general mortality of those people who had been within 1200 meters of the hypocenter of the atomic bomb.


Leukemia incidence (cases/10⁴ survivors/yr)
3000
2000
1000
0
200
400
600
800
1000
Estimated dose (rad)
H
N
Incidence in unexposed


Leukemia incidence (cases/10⁴ survivors)
15
10
5
0
Heavily exposed cases
(>100 rad)
All Japan
Nonexposed cases (<10 rad)
1950
1955
1960
1965
1970
1975
1980
1985

Human Radiation Experiments

- Plutonium injections started in April 1945 and continued for two years,involving 18 people with short remaining lifespans due to age or disease.
- The purpose of the experiment was not to observe radiation effects but to determine the excretion rate of plutonium over time for known intakes.
- None of the subjects died of causes that could be related to plutonium injections.
- The controversy arises as to whether the subjects were informed that they would be ingesting radioactive material.
- Other human radiation experiments involved tracer studies.

Tracer studies

- Forty-two people ingested iodine-131 and iodine-125 in order to improve diagnosis of thyroid disease and estimate doses due to radioactive fallout.

- In addition, tritium was ingested by three volunteers at Los Alamos.

Marshall Islands

- Marshall Island inhabitants suffered from the effects of radioactive fallout in 1954.
- There was an increase in children with mental retardation, childhood abnormalities, and childhood malignancy (leukemia).

Late Stochastic Effect - Genetic Mutation

- We have no substantive data on humans radiation-induced genetic mutations
- Müller's experiments on Drosophilia concluded that the radiation does not alter the quality of mutations but rather increases the frequency of them.
- *Doubling dose* is the dose of radiation that will produce twice the frequency of genetic mutations as would have been observed without the radiation.
- Data from mice leads to the conclusion that mammals have somecapacity to repair genetic damage.
- Most radiation-induced mutations are recessive, meaning they must be present in both male and female to produce the trait as discussed.

Summary (1)

- Acute radiation sickness is an early stochastic effect.
- Carcinogenesis and genetic mutations are a late stochastic effect.
- Stochastic effects are non-threshold, dose-response relationships.
- Occupational exposure has led to many late stochastic effects in people, such as lung cancer, bone cancer, and leukemia.

Summary (2)

- The three main syndromes of acute radiation exposure are cerebrovascular, gastrointestinal, and cardiovascular.
- According to the oncogene theory, the *ras* oncogene is mutated in 30% of all human cancers.
- According to the tumor suppressor theory, the p53 gene is mutated in 50% of all cancers.
- The follow up of Hiroshima and Nagasaki is among the primary sources of information for radiation exposure.